

Appl. No. 10/810,296
Dated April 17, 2008

Reply to Office action of April 5, 2008

Please replace paragraph [0012] with the following amended paragraph:

[0012] The present invention is a multiparameter screening method that is used for combining the contributions of atherosclerotic risk factors to the disease, predicting a total risk of the disease and a disease risk level, determining a primary cause in the disease, assessing a therapeutic efficacy and optimizing the therapeutic targets at the different stages of the disease in different individuals who require the diagnosis, prevention or treatment of atherosclerosis-related CHD or stroke, which comprises the following phases:

defining the normal as free from atherosclerosis-related coronary heart disease or stroke; the measured values refer to the quantities of atherosclerotic parameters to be measured; measuring, for an individual, having the measured values of these atherosclerotic parameters; the measuring, for an individual not having the disease, the normal values of these atherosclerotic parameters; determining the disease risks yielded by the differences between the measured values and the normal values of these atherosclerotic parameters; adding all the disease risks ~~together so as to yield~~

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containing a total risk of the disease;
determining a disease risk level containing the total risk of the disease;
selecting an atherosclerotic risk factor related to an atherosclerotic parameter that is the greatest contribution to the total risk so as to result in this risk factor as a primary therapy target of the disease;
determining a greater flux between the LDL mass transfer flux and the monocyte mass transfer flux so as to result in this greater flux as a primary cause in the disease;
selecting a greater concentration level between the LDL level in serum and the CRP level in blood plasma so as to result in this greater level as a secondary therapy target of the disease;
calculating a relative ratio between the current total risk from the currently measured values of these atherosclerotic parameters and the previous total risk from previously measured values of these parameters so as to yield this ratio as a therapeutic efficacy of the disease; and
repeating the above-mentioned methods until the disease risk level is reduced to a normal level for the individual who requires the therapy to prevent or to treat atherosclerosis-related CHD or stroke.

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the above-mentioned methods are written as an executable computer program named the MMA.exe to be installed into a general purpose digital computer device to accomplish said methods.

outputting the total risk, the risk level, the primary cause, the therapeutic target and the therapeutic efficiency to a display or a user.

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Please replace paragraph [0031] with the following amended paragraph:

[0031] Step 3.1:

Substituting a measured value $[(c_m)]Cm_1$ of the LDL concentration parameter into (1.1)

yields $[(J_m = Hc_m^{\frac{11}{9}})] Jm_1 = HCm_1^{\frac{11}{9}}$

where $H = A(v^3 D^{16})^{\frac{1}{27}} \left(\frac{gcosa + fu}{z} \right)^{\frac{2}{9}}$ and $H_e = 1$ in A;

substituting a normal value $[(c_n)]Cn_1$ of the LDL concentration into (1.1) yields

$[(J_n = Hc_n^{\frac{11}{9}})] Jn_1 = HCn_1^{\frac{11}{9}}$; and

calculating $[(\frac{J_m - J_n}{J_n})] \frac{Jm_1 - Jn_1}{Jn_1}$ where $c_m \geq c_n$

yields:

$$[(R_1 = \left(\frac{c_m}{c_n} \right)^{\frac{11}{9}} - 1)] R_1 = \left(\frac{Cm_1}{Cn_1} \right)^{\frac{11}{9}} - 1 \quad (1)$$

where $Cm_1 \geq Cn_1$ and R_1 is the disease risk caused by the LDL concentration parameter related to the atherosclerotic risk factors being an elevated LDL level in human serum, hypercholesterolemia, high-fat diet, or other risk factors that increase in the LDL

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level.

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Please replace paragraph [0032] with the following amended paragraph:

[0032] Step 3.2:

Substituting a measured value $[[c_m]] \underline{Cm_2}$ of the CRP concentration parameter into (1.1)

yields $[[J_m = Hc_m^{\frac{11}{9}}]] Jm_2 = HCm_2^{\frac{11}{9}}$ where

$$H = A(v^3 D^{16})^{\frac{1}{27}} \left(\frac{g \cos \alpha + f u}{z} \right)^{\frac{2}{9}};$$

substituting a normal value $[[c_n]] \underline{Cn_2}$ of the CRP concentration into (1.1) yields

$[[J_n = Hc_n^{\frac{11}{9}}]] Jn_2 = HCn_2^{\frac{11}{9}}$; and

calculating $[[\frac{J_m - J_n}{J_n}]] \underline{\frac{Jm_2 - Jn_2}{Jn_2}}$ where $c_m \geq c_n$

yields:

$$[[R_2 = \left(\frac{c_m}{c_n} \right)^{\frac{11}{9}} - 1]] R_2 = \left(\frac{Cm_2}{Cn_2} \right)^{\frac{11}{9}} - 1 \quad ([2] 2.1)$$

where $\underline{Cm_2 \geq Cn_2}$ and R_2 is the disease risk caused by the CRP concentration parameter related to the atherosclerotic risk factors being the systemic inflammation, infectious agents, an elevated CRP level in human blood plasma, or other risk factors that increase the CRP level.

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Please replace paragraph [0033] with the following amended paragraph:

[0033] Step 3.3:

Determining an equivalent factor F between the R_1 in Step 3.1 and the R_2 in Step 3.2, which comprises the following two methods:

1. The first method:

Substituting the LDL diffusion coefficient D_L into (1.1) yields $J_x = M D_L^{\frac{16}{27}}$ where

$M = A c^{\frac{11}{9}} v^{\frac{3}{27}} \left(\frac{g \cos \alpha + f u}{z} \right)^{\frac{2}{9}}$ and J_x = the LDL mass transfer flux;

substituting the CRP diffusion coefficient D_c into (1.1) yields $J_y = M D_c^{\frac{16}{27}}$ where J_y = the CRP mass transfer flux;

taking $J_y D_L^{\frac{16}{27}} = J_x D_c^{\frac{16}{27}}$ so as to yield:

$$J_y = J_x F \quad (G)$$

where the equivalent factor $F = \left(\frac{D_c}{D_L} \right)^{\frac{16}{27}}$; and

according to (G), the equation ([2]2.1) in Step 3.2 is rewritten as

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$$[[R_2 = F \left(\left(\frac{c_m}{c_n} \right)^{\frac{11}{9}} - 1 \right)]] R_2 = F \left(\left(\frac{Cm_2}{Cn_2} \right)^{\frac{11}{9}} - 1 \right) \quad ([[3]]_2)$$

where Cm₂ ≥ Cn₂ and the disease risk R₂ caused by the difference between the measured value [[c_m]]Cm₂ and normal value [[c_n]]Cn₂ of the CRP concentration parameter corresponds to the disease risk R₁ caused by the LDL concentration parameter by means of ([[3]]_2).

2. The secondary method:

The equivalent factor F = 0.66, which will be yielded in the Step five of the DETAILED DESCRIPTION OF THE INVENTION.

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Please replace paragraph [0034] with the following amended paragraph:

[0034] Step 3.4:

Substituting a measured value $\underline{[P_m]} P_{m_3}$ of the blood systolic pressure parameter into (1.2)

yields $\underline{[J_m = H_p p_m^{\frac{1}{3}}]} J_{m_3} = H_p P_{m_3}^{\frac{1}{3}}$ where

$$H_p = B c^{\frac{11}{9}} T^{\frac{16}{27}} a^{\frac{2}{3}} f^{\frac{2}{9}} z^{-\frac{2}{9}};$$

substituting a normal value $\underline{[P_n]} P_{n_3}$ of the systolic pressure into (1.2) yields

$\underline{[J_n = H_p p_n^{\frac{1}{3}}]} J_{n_3} = H_p P_{n_3}^{\frac{1}{3}}$; and

calculating $\underline{[\frac{J_m - J_n}{J_n}]} \frac{J_{m_3} - J_{n_3}}{J_{n_3}}$ where $P_m \geq P_n$

yields:

$$\underline{[[R_4 = \left(\frac{P_m}{P_n}\right)^{\frac{1}{3}} - 1]] R_3 = \left(\frac{P_{m_3}}{P_{n_3}}\right)^{\frac{1}{3}} - 1}} \quad ([4] \underline{3})$$

where $\underline{P_{m_3} \geq P_{n_3}}$ and $\underline{[R_4]} R_3$ is the disease risk caused by the systolic pressure parameter related to atherosclerotic risk factors being an elevated level of the systolic pressure, family history of hypertension, or other risk factors that increase in the systolic pressure.

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Please replace paragraph [0035] with the following amended paragraph:

[0035] Step 3.5:

Substituting a measured value $\left[\left[P_m\right]\right]Pm_4$ of the blood diastolic pressure parameter into (1.2)

yields $\left[\left[J_m = H_p P_m^{\frac{1}{3}}\right]\right]Jm_4 = H_p Pm_4^{\frac{1}{3}}$ where

$$H_p = Bc^{\frac{11}{9}} T^{\frac{16}{27}} a^{\frac{2}{3}} f^{\frac{2}{9}} z^{-\frac{2}{9}};$$

substituting a normal value $\left[\left[P_n\right]\right]Pn_4$ of the diastolic pressure into (1.2) yields

$\left[\left[J_n = H_p P_n^{\frac{1}{3}}\right]\right]Jn_4 = H_p Pn_4^{\frac{1}{3}}$; and

calculating $\left[\left(\frac{J_m - J_n}{J_n}\right)\right] \frac{Jm_4 - Jn_4}{Jn_4}$ where $P_m \geq P_n$

yields:

$$\left[\left[R_3 = \left(\frac{P_m}{P_n}\right)^{\frac{1}{3}} - 1\right]\right] R_4 = \left(\frac{Pm_4}{Pn_4}\right)^{\frac{1}{3}} - 1 \quad ([5]4)$$

where $Pm_4 \geq Pn_4$ and $\left[\left[R_5\right]\right]R_4$ is the disease risk caused by the diastolic pressure parameter related to the atherosclerotic risk factors being an elevated level of the diastolic pressure, the family history of hypertension, or other risk factors that

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increase in the diastolic pressure.

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Please replace paragraph [0036] with the following amended paragraph:

[0036] Step 3.6:

Substituting a measured value $[[f_m]] \underline{Fm_5}$ of the heart rate parameter into (1.2) yields

$$[[J_m = H_f f_m^{\frac{2}{9}}]] \underline{Jm_5} = H_f \underline{Fm_5}^{\frac{2}{9}} \text{ where } H_f = Bc^{\frac{11}{9}} T^{\frac{16}{27}} a^{\frac{2}{3}} p^{\frac{1}{3}} z^{-\frac{2}{9}};$$

substituting a normal value $[[f_n]] \underline{Fn_5}$ of the heart rate into (1.2) yields

$$[[J_n = H_f f_n^{\frac{2}{9}}]] \underline{Jn_5} = H_f \underline{Fn_5}^{\frac{2}{9}}; \text{ and}$$

calculating $[[\frac{J_m - J_n}{J_n}]] \underline{\frac{Jm_5 - Jn_5}{Jn_5}}$ where $f_m \geq f_n$

yields:

$$[[R_6 = \left(\frac{f_m}{f_n}\right)^{\frac{2}{9}} - 1]] \underline{R_5} = \left(\frac{Fm_5}{Fn_5}\right)^{\frac{2}{9}} - 1 \quad ([6]5)$$

where $\underline{Fm_5} \geq \underline{Fn_5}$ and $[[R_6]] \underline{R_5}$ is the disease risk caused by the heart rate parameter related to the atherosclerotic risk factors being an elevated level of the heart rate, smoking cigarette, emotional factors such as depression, or other risk factors that increase the heart rate.

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Please replace paragraph [0037] with the following amended paragraph:

[0037] Step 3.7:

Substituting a measured value $[[a_m]] \underline{Am_6}$ of the radius parameter of arterial vessel into

(1.2) yields $[[J_m = H_a a_m^{\frac{2}{3}}]] \underline{Jm_6} = H_a Am_6^{\frac{2}{3}}$ where

$$H_a = B c^{\frac{11}{9}} T^{\frac{16}{27}} f^{\frac{2}{9}} p^{\frac{1}{3}} z^{-\frac{2}{9}},$$

substituting a normal value $[[a_n]] \underline{An_6}$ of the arterial radius into (1.2) yields

$[[J_n = H_a a_n^{\frac{2}{3}}]] \underline{Jn_6} = H_a An_6^{\frac{2}{3}}$; and

calculating $[[\frac{J_m - J_n}{J_n}]] \underline{\frac{Jm_6 - Jn_6}{Jn_6}}$ where $a_m \geq a_n$

yields:

$$[[R_7 = \left(\frac{a_m}{a_n}\right)^{\frac{2}{3}} - 1]] \underline{R_6} = \left(\frac{Am_6}{An_6}\right)^{\frac{2}{3}} - 1 \quad ([[[7]] \underline{6})$$

where $\underline{Am_6} \geq \underline{An_6}$ and $[[R_7]] \underline{R_6}$ is the disease risk caused by the arterial radius parameter related to atherosclerotic risk factors being the increased radius of arterial vessels at the lesion-prone sites, or other risk factors that increase the arterial radius.

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Please replace paragraph [0038] with the following amended paragraph:

[0038] Step 3.8:

Substituting a measured value $[[T_m]] \underline{Tm_7}$ of the plasma temperature parameter into (1.2)

yields $[[J_m = H_T T_m^{27}]] \underline{Jm_7 = H_T Tm_7^{27}}$ where

$$H_T = B c^{\frac{11}{9}} a^{\frac{2}{3}} f^{\frac{2}{9}} p^{\frac{1}{3}} z^{-\frac{2}{9}},$$

substituting a normal value $[[T_n]] \underline{Tn_7}$ of the plasma temperature into (1.2) yields

$[[J_n = H_T T_n^{27}]] \underline{Jn_7 = H_T Tn_7^{27}}$; and

calculating $[[\frac{J_m - J_n}{J_n}]] \underline{\frac{Jm_7 - Jn_7}{Jn_7}}$ where $T_m \geq T_n$

yields:

$$[[R_8 = \left(\frac{T_m}{T_n}\right)^{\frac{16}{27}} - 1]] \underline{R_7 = \left(\frac{Tm_7}{Tn_7}\right)^{\frac{16}{27}} - 1} \quad ([[[8]]] 7)$$

where $\underline{Tm_7 \geq Tn_7}$ and $[[R_8]] \underline{R_7}$ is the disease risk caused by the plasma temperature parameter related to the atherosclerotic risk factors being the elevated temperature of the blood plasma in the region of the lesion-prone sites, the elevated body temperature-related diseases, or other risk

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factors that increase the plasma temperature.

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Please replace paragraph [0039] with the following
amended paragraph:

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[0039] Step 3.9:

Substituting a measured value $[\alpha_m]$ of the angle parameter into (1.3) yields

$$[\ [J_m = H_a (\cos \alpha_m)^{\frac{2}{9}}]] Jm_8 = H_a (\cos \alpha m_8)^{\frac{2}{9}} \text{ where}$$

$$H_a = Ec^{\frac{11}{9}} D^{\frac{16}{27}} z^{-\frac{2}{9}};$$

substituting a normal value $[\alpha_n]$ of the angle into (1.3) yields

$$[\ [J_n = H_a (\cos \alpha_n)^{\frac{2}{9}}]] Jn_8 = H_a (\cos \alpha n_8)^{\frac{2}{9}}; \text{ and}$$

$$\text{calculating } [\frac{J_m - J_n}{J_n}] \frac{Jm_8 - Jn_8}{Jn_8} \text{ where } \alpha_n \geq \alpha_m$$

yields:

$$[\ [R_9 = \left(\frac{\cos \alpha_m}{\cos \alpha_n} \right)^{\frac{2}{9}} - 1]] R_8 = \left(\frac{\cos \alpha m_8}{\cos \alpha n_8} \right)^{\frac{2}{9}} - 1 \quad ([9]8)$$

where $\alpha n_8 \geq \alpha m_8$, and $[(R_9)]R_8$ is the disease risk caused by the angle parameter related to the atherosclerotic risk factors being the reduced size of the angle between the gravity and the average velocity of blood fluid in the region of the lesion-prone sites, an acute daughter angle of arterial

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bifurcation, or other risk factors that
reduce the angle size.

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Please replace paragraph [0040] with the following amended paragraph:

[0040] Step 3.10:

Substituting a measure value $[[Z_m]] \underline{Zm_9}$ of the axial position parameter of the diffusional

flux into (1.1) yields $[[J_m = H_z z_m^{\frac{2}{9}}]] \underline{Jm_9 = H_z Zm_9^{\frac{2}{9}}}$

where $H_z = A c^{\frac{11}{9}} (v^3 D^{16})^{\frac{1}{27}} (g \cos \alpha + f u)^{\frac{2}{9}}$;

substituting a normal value $[[Z_n]] \underline{Zn_9}$ of the diffusional length into (1.1) yields

$[[J_n = H_z z_n^{\frac{2}{9}}]] \underline{Jn_9 = H_z Zn_9^{\frac{2}{9}}}$; and

calculating $[[\frac{J_m - J_n}{J_n}]] \underline{\frac{Jm_9 - Jn_9}{Jn_9}}$ where $\underline{z_m \leq z_n}$

yields:

$$[[R_{10} = \left(\frac{Z_n}{Z_m} \right)^{\frac{2}{9}} - 1]] \underline{R_9 = \left(\frac{Zn_9}{Zm_9} \right)^{\frac{2}{9}} - 1} \quad ([10]9)$$

where $\underline{Zn_9 \geq Zm_9}$, and $[[R_{10}]] \underline{R_9}$ is the disease risk caused by the axial position parameter of diffusional flux related to the atherosclerotic risk factors being the reduced axial position of the diffusional flux along the inner arterial wall at the lesion-prone sites, or other risk factors that reduce the axial

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position.

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Please replace paragraph [0041] with the following amended paragraph:

[0041] Step four:

Adding the R_1 in step 3.1 and the R_2 in step 3.3 through the $[[R_{10}]]R_9$ in step 3.10 ~~together so as to yield~~ containing a total risk of the disease comprising;

a current total risk of the disease caused by the differences between the currently measured values and the normal values of the atherosclerotic parameters;

a previous total risk of the disease caused by the differences between the previously measured values and the normal values of the atherosclerotic parameters.

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Please replace paragraph [0042] with the following amended paragraph:

[0042] Step five:

Determining a disease risk level containing the total risk of the disease in Step four comprising;

considering the range of the LDL concentration in serum from 100 mg/dL to 300 mg/dL; and

dividing the LDL risk level into the six risk sublevels at intervals of 33 mg/dL according to the guideline of LDL risk level given by the expert panels on US National Cholesterol Education Program;

considering the range of CRP concentration in blood plasma from 1.0 mg/L to 4.0 mg/L; and

dividing the CRP risk level into the six risk sublevels at intervals of 0.5 mg/L according to the guideline of the CRP risk level given by American Heart Association;

calculating the ratio between the LDL range and the CRP range yields an equivalent factor $F = 2/3 = 0.66$;

Substituting the $F = 0.66$, $[[c_n]]Cn_2 = 1.0 \text{ mg/L}$ and the six CRP measured values that equal the

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interval values of six CRP risk sublevels into the equation ($[[3]]_2$) in Step 3.3 respectively; and

calculating ($[[3]]_2$) yields the six disease risks as the interval values of the six disease risk sublevels respectively;

doubling these interval values so as to result in the following seven disease risk sublevels caused by combining the LDL flux and the monocyte flux: $0.84 \geq$ first disease risk level ≥ 0.00 , $1.75 \geq$ second disease risk level > 0.84 , $2.70 \geq$ third disease risk level > 1.75 , $3.70 \geq$ fourth disease risk level > 2.70 , $4.70 \geq$ fifth disease risk level > 3.70 , $5.80 \geq$ sixth disease risk level > 4.70 and seventh disease risk level > 5.80 ; and selecting a disease risk level containing the total risk of the disease in Step four from among seven of the disease risk sublevels.

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Please replace paragraph [0048] with the following amended paragraph:

[0048] Step eleven: These methods in Step three through Step nine are written as an executable computer program named the MMA.exe to be installed into a general purpose digital computer device to accomplish these methods and to output a result of the method of this invention, call the screening report consisting a total risk, a risk level, a primary cause, a primary therapy target, a secondary therapy target and a therapeutic efficiency, to the individual who requires the therapy to prevent or treat atherosclerosis-related CHD or stroke.